Respiratory Diseases among U.S. Military Personnel: Countering Emerging Threats

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Emerging respiratory disease agents, increased antibiotic resistance, and the loss of effective vaccines threaten to increase the incidence of respiratory disease in military personnel. We examine six respiratory pathogens (adenoviruses, influenza viruses, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Mycoplasma pneumoniae,* and *Bordetella pertussis*) and review the impact of the diseases they cause, past efforts to control these diseases in U.S. military personnel, as well as current treatment and surveillance strategies, limitations in diagnostic testing, and vaccine needs.

Respiratory infections, the most common cause of acute infectious disease in U.S. adults (1), are also the leading cause of outpatient illness and a major cause (25% to 30%) of infectious disease hospitalization in U.S. military personnel (2,3). Because of crowded living conditions, stressful working environment, and exposure to respiratory pathogens in disease-endemic areas, military trainees and newly mobilized troops are at particularly high risk for respiratory disease epidemics (2, 4-6). For example, before vaccines were used, more than 80% of military trainees had respiratory infections, and as many as 20% were hospitalized during the 2 months of recruit training (7). Although respiratory disease control is improved, epidemics continue to occur, and respiratory disease in military trainees continues to exceed that in U.S. civilian adults (Figure 1). The recent loss of adenovirus vaccine (types 4 and 7) production, changes in the susceptibility of pathogens to antimicrobial drugs, and emerging respiratory pathogens threaten to increase the military population's vulnerability to respiratory diseases.

We review the changing epidemiology and control of six major respiratory disease pathogens of special concern to the military.

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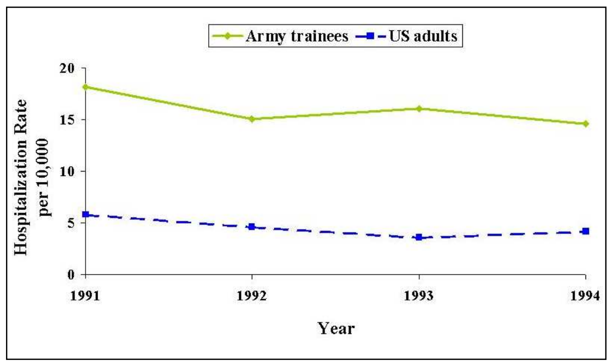

Figure 1. Hospitalization rates for acute respiratory disease per 10,000 persons, 1991 to 1994: U.S. army recruits vs. young adults in U.S. nonfederal hospitals. U.S. army recruit estimates are converted from percentage febrile acute respiratory disease rates per 100 trainee-week figures (8). On average, recruits were 19 years old. U.S. national nonfederal estimates were taken from first-listed diagnoses with the International Classification of Diseases codes 460 to 466 (9) among persons of ages 15 to 44 years (10-13).

Adenoviruses

Respiratory disease agents discovered in adenoidal tissue in U.S. soldiers in the 1950s were associated with rhinitis, pharyngitis, conjunctivitis, pneumonitis, and atypical pneumonia and were subsequently designated as adenoviruses (14). In 1958, adenoviruses caused hospitalization of an estimated 10% of military recruits (15). Adenoviral disease was highest during winter, accounting for 90% of all recruits hospitalized with pneumonia (16,17) and 72% of all respiratory disease (17). Military recruits had a greater chance of acquiring adenoviral infections than similar civilian populations, with most infections occurring during the first 3 weeks of military training (16,18,19). Of the 47 adenoviral serotypes, types 4 and 7 accounted for most military respiratory disease epidemics. A 1965 study of a typical epidemic at Fort Dix, New Jersey, established the need for vaccines (20).

In 1971, the Department of Defense (DoD) began routine use of live, enteric-coated types 4 and 7 vaccines, which have remained very effective (6). Vaccine development for other serotypes that cause only infrequent epidemics was begun, but no vaccine became licensed. Recently, the sole manufacturer of the adenovirus type 4 and type 7 vaccines ceased production, so neither vaccine is available. The unavailability of adenovirus vaccines threatens a sharp increase in numbers of acute respiratory disease epidemics in the military, especially among recruits (6). Recently, two recruit centers where the vaccines were not available had large acute respiratory disease epidemics (21,22).

The ecologic and pathologic features of adenoviruses in military populations are poorly understood (23,24). Most available surveillance data are more than 20 years old (7,20). To better understand the distribution of adenovirus serotypes, risk for infection, and agent dynamics following vaccine loss, triservice adenovirus surveillance has been established at five military training centers (Figure 2) (25). Early data indicate that types 4 and 7 vaccines remain effective, but nonvaccine serotypes are prevalent and should be considered in new vaccine development strategies. More than 55% of 3,212 throat cultures from symptomatic trainees from October 1996 to May 1998 yielded adenoviruses. Most prevalent were types 4 (46%), 7 (32%), 3 (13%), and 21 (5%). Among trainees with acute respiratory infection symptoms, nonvaccinated personnel were at greater risk of having a culture positive for adenovirus types 4 and 7 (odds ratio = 41.2; 95% confidence interval = 18.7 to 113.2) than vaccinated personnel. Capability to isolate and identify adenoviruses has improved, but simple rapid molecular diagnostic techniques have not yet been developed.

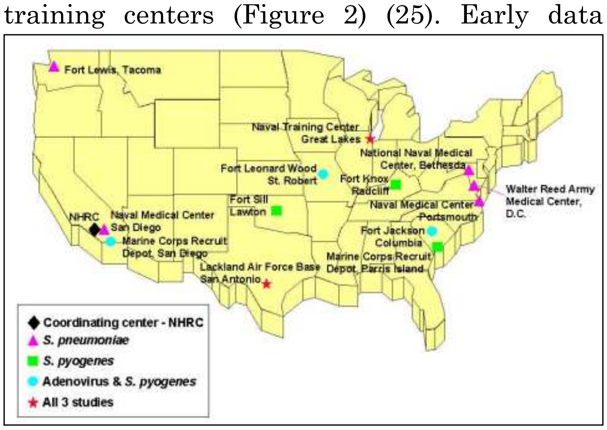

Figure 2. Department of Defense medical treatment facilities and recruit training camps participating in surveillance for emerging respiratory disease pathogens: invasive *Streptococcus pneumoniae* (typing and antibiotic sensitivity studies); *Streptococcus pyogenes* (typing and antibiotic sensitivity studies); and adenovirus (typing studies).

Influenza

Since an annual influenza vaccine policy was adopted for active-duty personnel in the 1950s, massive influenza epidemics have largely ended. However, the potential for illness and death due to new viral strains remains. During the last 3 months of 1918, an influenza A pandemic affected 106,897 (18.8%) of 569,470 navy personnel, with an estimated case-fatality rate of 4.5%. The case-fatality rate was particularly high among military trainees, especially those who had pneumonia. For example, during a 30-day period beginning in September 1918, 9,623 (21.5%) of 44,605 navy trainees (Illinois) had influenza, and 924 died; the case-fatality rate was highest (48%) among those with pneumonia (26). At autopsy, streptococcal organisms were often associated with pneumonia, which suggests that pathogens in the training camps may have exacerbated the influenza illnesses and deaths during this pandemic.

Even with annual use of influenza vaccine, laboratory-based surveillance is critical. During February 1996, a U.S. navy ship with a 600-person crew had an estimated 42% influenza A attack rate, although more than 95% of the crew had received the annual influenza vaccine (K. Earhart, pers. comm.). The annual vaccine for that winter (A/Johannesburg/33/94-like [H3N2] and A/Texas/36/91-like [H1N1]) did not protect against the A/Wuhan/359/95 [H3N2] strain that infected the crew.

The recent outbreak of H5N1 influenza A in Hong Kong prompted a review of capability to detect new influenza strains (27); only the air force was conducting a laboratory-based surveillance program (28). Since the Hong Kong outbreak, a cooperative global influenza surveillance network has been formed. Worldwide, more than 20 medical treatment facilities and laboratories from all services are collecting influenza isolates for typing (Figure 3) (29). Additionally, in the United States, military training sites at high risk for influenza are monitored so that epidemics might be quickly detected. This early warning system allows public health officials to modify vaccine antigens, use antiviral drugs, and take other measures to reduce illness.

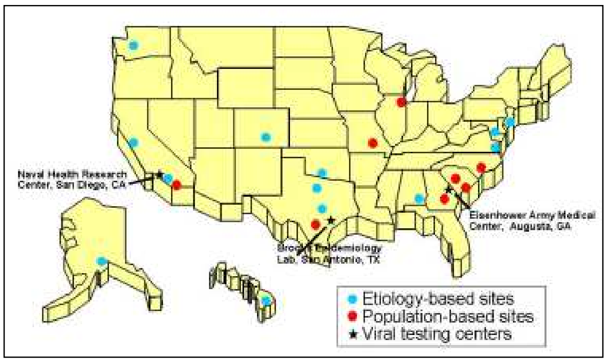

Figure 3. Military sites in the United States participating in Department of Defense influenza surveillance. The focus of surveillance at etiology-based sites is to determine the viral causes of influenzalike illnesses; the focus of population-based sites is to closely monitor for influenzalike illness epidemics.

Streptococcus pneumoniae

Before penicillin was introduced, complications of *S. pneumoniae* infections were frequent and often fatal. Large epidemics of pneumonia occurred in crowded military populations, particularly after influenza outbreaks, especially during winter. In 1918, a 1-month epidemic of *S. pneumoniae* in a military camp in Illinois resulted in 2,349 hospital admissions with a 50% death rate (30). From the 1960s to the 1980s, military epidemics of pneumococcal disease were very rare. However, in recent years, military pneumococcal epidemics have occurred in southern California (31), in North Carolina (32), and among a ship's crew in the Mediterranean Sea (4).

S. pneumoniae infections have various clinical features, including pneumonia, meningitis, empyema, bacteremia, conjunctivitis, sinusitis, arthritis, and otitis media. Since the introduction of penicillin, epidemics of respiratory disease caused by *S. pneumoniae* are much less frequent but remain a threat. To counter outbreaks, the military has used mass prophylaxis with benzathine penicillin G (1.2 million units) intramuscularly (31). However, the efficacy of this intervention and its impact on antibiotic resistance have not been fully evaluated (33). In 1991, the Armed Forces Epidemiological Board recommended pneumococcal vaccine (23-valent polysaccharide) for populations at high risk for *S. pneumoniae* infection. However, because of the cost and uncertainty about efficacy in healthy young adults, the vaccine is given only to trainees at one marine corps installation.

During the last 20 years, penicillin-resistant *S. pneumoniae* (intermediate and highly resistant strains), as well as multidrug-resistant strains, have been reported with increasing frequency throughout the world. Recently, investigators from Korea reported that 70% of 131 clinical civilian pneumococcal isolates were penicillin-resistant (34). On the basis of limited surveillance data, the public health threat of penicillin-resistant *S. pneumoniae* to U.S. military personnel and their dependents is increasing (35). Walter Reed Army Medical Center, Washington, D.C., reported an increase in the percentage of penicillin-resistant *S. pneumoniae* isolates from 0% in 1990 to 36.2% in 1994 (36).

In winter 1989-90, an outbreak among marine trainees at Camp Pendleton, California, resulted in 128 reported cases of pneumonia, one of the largest epidemics since the development of antibiotics. The epidemic triggered mass prophylaxis with benzathine penicillin G and administration of pneumococcal vaccine (31). Soon after, other smaller epidemics of pneumococcal pneumonia occurred among U.S. army rangers (32) and among the crews of two navy ships in Italian waters (4). As we write (March 1999), another pneumococcal pneumonia outbreak among army trainees is under epidemiologic investigation. These recent pneumococcal epidemics may be evidence of a changing epidemiologic threat. Pneumococcal pneumonia, which was checked when antibiotics became available in the 1950s, seems to have reemerged.

Increasing antibiotic resistance and epidemics prompted surveillance for invasive

S. pneumoniae disease (Figure 2). Early data from patients hospitalized in military hospitals in the United States are consistent with data from civilian U.S. populations. On average, 35% of isolates have full or partial resistance to penicillin (35,37). Thus far, nearly all invasive isolates are of types included in the 23-valent vaccine. A cost-effectiveness analysis projected that using this vaccine among new navy and marine corps personnel would result in a lifetime savings of approximately $9 million (38).

Streptococcus pyogenes

U.S. military populations have frequently had large *S. pyogenes*–caused epidemics of pharyngitis and acute rheumatic fever, accompanied by other concomitant diseases, such as pneumonia, sepsis, polymyositis, necrotizing fasciitis, scarlet fever, and glomerulonephritis (5,39). Historically, because of cramped living conditions, military recruits have been at high risk for streptococcal disease (2,5,39,40). Illness was especially high in World War II, with the navy reporting approximately one million streptococcal infections and more than 21,000 cases of acute rheumatic fever (5,41).

In 1948, Massell et al. (42) reported that the treatment of acute pharyngitis infection with oral penicillin prevented acute rheumatic fever. Further studies confirmed the effectiveness of a single intramuscular injection of benzathine penicillin G in preventing a broad range of acute and chronic sequelae of streptococcal infections (5,40,43). These early successes led to mass antimicrobial prophylaxis with benzathine penicillin G in training populations at high risk to interrupt and prevent outbreaks of acute disease and their sequelae (44). This control strategy was generally very effective. However, a 1989 epidemic of *S. pyogenes* pharyngitis among marine corps trainees demonstrated that benzathine penicillin G prophylaxis for nonpenicillin-allergic trainees alone might not protect against epidemics in closely contained populations, especially those with longer training periods, as unprotected penicillin-allergic recruits may serve as *S. pyogenes* reservoirs. This finding led to the navy's adoption of oral erythromycin as prophylactic therapy for penicillin-allergic recruits (39,45). Another study has shown that 500 mg of azithromycin taken orally each week is, by serologic evidence, an effective prophylactic intervention against *S. pyogenes* (33).

Since the development of antibiotic prophylaxis, civilian and military epidemics of *S. pyogenes* disease have declined and then reemerged (39,46,47). Epidemics of acute rheumatic fever have occurred throughout the United States (46-48). In addition, an estimated 10,000 cases of severe *S. pyogenes* disease, such as necrotizing fasciitis and streptococcal toxic shock, occur nationwide each year (49-52). Increases in invasive streptococcal disease among some U.S. populations have been attributed to changes in the prevalence of virulent strains of *S. pyogenes*(53).

Although antibiotic prophylaxis remains effective, *S. pyogenes* persists as a leading cause of bacterial respiratory illness among military personnel (5,39,47,48,54). Risk factors associated with *S. pyogenes* infection include recent entry to the military, crowding, lack of prophylaxis, close contact with an *S. pyogenes* carrier, and close contact with a trainee who has not received antibiotic prophylaxis (39).

Prophylactic use of oral erythromycin or azithromycin may promote macrolide resistance among endemic streptococci. The Naval Medical Center, San Diego, California, found 5(10%) of 50 consecutive clinical isolates collected during March and April 1997 resistant to erythromycin. While frequently reported in Europe and Japan, macrolide resistance has been uncommon in U.S. military populations (T. Ferguson, R. Haberberger, pers. comm.) and infrequent in isolates from civilians in the United States (55).

Triservice surveillance has been established to define antibiotic resistance patterns and determine which serotypes of *S. pyogenes* are causing clinical disease (Figure 2). Data from eight sentinel military medical treatment facilities will be used to monitor resistance and develop alternate prophylactic strategies, rapid diagnostic tests, and vaccines.

Mycoplasma pneumoniae

During World War II, acute pneumonia in military personnel was frequently milder than lobar pneumonia. Chest radiographs showed substantial pulmonary involvement, yet patients did not have high fever, pleuritic chest pain, or rigors characteristic of pneumonia caused by *S. pneumoniae*. In 1943, these infections were recognized as primary atypical pneumonia, which accounted for an estimated 68% of atypical pneumonias among marine trainees (56) and infected as many as 44% of recruits over a 3-month training period (57). In 1944, samples from a patient with atypical pneumonia showed *M. pneumoniae* (57,58), and soon thereafter, *M. pneumoniae* was identified as an important cause of acute respiratory disease in U.S. military personnel (59).

A common cause of pharyngitis and bronchopneumonia, *M. pneumoniae* may also cause fulminant pneumonia, cardiac disease, arthritis, dermatologic conditions, and central nervous system disease (60). Crowded military populations are at particularly high risk for infection. In the 1970s, up to 57% of U.S. recruits had evidence of acute infection (61), and from the 1960s through the 1990s, as many as 56% of pneumonia cases among recruits were due to *M. pneumoniae* (62-64). Because culture and diagnostic tests for *M. pneumoniae* are not commonly available at military facilities, *M. pneumoniae* is often not recognized, and ineffective antibiotics are prescribed (62).

Few options are available for combating *M. pneumoniae* epidemics. More than 25 years ago, several studies suggested that preexisting antibody titers might prevent infection (65,66), and vaccine candidates were tested with mixed success (64,67,68). In 1965, preventing disease with a 10-day course of oxytetracycline (69) (4 times a day) among close contacts was successful but impractical. More recently, weekly oral azithromycin (500 mg) had a 64% protective efficacy (by serologic tests) against *M. pneumoniae* in U.S. marines (33).

Reliable diagnostic tests and enhanced surveillance efforts are needed to assess the epidemiology and impact of *M. pneumoniae* on military populations. With the exception of serologic tests, few rapid diagnostic tests are commercially available.

Bordetella pertussis

Before vaccines were available, *B. pertussis* caused considerable illness in children. With the effectiveness of whole-cell childhood vaccines, disease incidence increased among older children and adults, whose childhood vaccine immunity had waned (70-74). *B. pertussis* infection in adults, while generally mild (75), can be incapacitating. No pertussis vaccines are available for adults.

B. pertussis also affects military populations; a 1989 study of marine trainees who reported 7 or more days of cough showed that 18% had acute *B. pertussis* infection (73). The potential for military epidemics of *B. pertussis* is demonstrated by outbreaks among other confined populations, such as those receiving general or institutionalized medical care, which have attack rates as high as 91% (76,77). Infection in adults is often difficult to verify since culture and polymerase chain reaction diagnostic tests may be negative (73). While often used epidemiologically, serologic methods are not standardized, nor are they routinely performed by clinical laboratories (78). Hence, many epidemics are monitored by clinical case definitions.

Some clinicians have observed a prophylactic benefit in administering oral erythromycin to close contacts of patients (78). However, erythromycin prophylaxis is not without side effects, and its value has been questioned (76,79). New acellular pertussis vaccines, now approved only for use among infants and children, are being studied for use in adults (80).

Research and Disease Control

Trainees entering military service receive influenza vaccine and adenovirus types 4 and 7 vaccines when available. Mass antibiotic chemoprophylaxis is also often used to prevent acute respiratory disease and control epidemics, particularly those caused by *S. pyogenes* infections. After initial training, military personnel receive annual influenza vaccine and periodic tuberculosis screening (Table).

Almost all respiratory illnesses, including pneumonia, are treated empirically (4,62), often with penicillin or a macrolide (62). Without accurate laboratory diagnoses and an early warning system to detect changes in acute respiratory disease rates and antibiotic resistance, more respiratory disease epidemics are likely to occur in military populations. A Global Emerging Infections Surveillance and Response System has been established to address this problem. Surveillance data will be used to direct acute respiratory disease research, training, and education. Under the system, DoD has recently established modest surveillance programs for influenza, adenovirus, *S. pyogenes*, and

Table. Current capacity to control respiratory pathogens at most military medical treatment facilities, United States

Pathogen	Culture	Rapid diagnostic tests	Prophylaxis	Vaccine[a]
Streptococcus pyogenes	Available	Antigen detection available and used	Benzathine penicillin G (5), erythromycin (45), or azithromycin (33)	Needed
Streptococcus pneumoniae	Available but not sensitive	Needed	Azithromycin (33)	Available but seldom used among military personnel
Mycoplasma pneumoniae	Not available	Serologic tests are available	Azithromycin (33)	Needed
Influenza	Not available[b]	Needed	Amantadine	Vaccine available and routinely used
Adenovirus	Not available[b]	Needed	Not available	Types 4 and 7 vaccines effective but not available
Bordetella pertussis	Available but not sensitive	Needed	Erythromycin prophylaxis is of questionable value (79)	Needed

[a]While a number of civilian populations, such as the institutionalized, may have similar needs these vaccine needs are particularly urgent for crowded military trainees.
[b]Some medical treatment facilities have access to culture support.

S. pneumoniae at a number of U.S. military recruit training camps and special facilities, in collaboration with other federal, state, and civilian organizations. Recruit sites were chosen for their long history of respiratory disease epidemics and the possibility of monitoring the impact of mass antibiotic prophylaxis. Tertiary referral medical centers were chosen to participate because they were more likely to detect unusual and antibiotic-resistant strains of respiratory pathogens. Limited samples of clinical influenza A, adenovirus, *S. pyogenes,* and *S. pneumoniae* isolates are being studied. However, new diagnostic tools and vaccines are still needed (Table).

Conclusions

Military personnel, because of crowding and unique stressors, are subject to respiratory disease epidemics. Their risk often exceeds that of their civilian peers. Adenovirus, influenza virus, *S. pyogenes*, *S. pneumoniae*, and *B. pertussis* are particularly problematic. Pathogen control measures, many of which were developed more than 20 years ago, are threatened by loss of vaccine production, changes in pathogen virulence, changes in pathogen antibiotic sensitivity, changes in population immunity, and lack of laboratory infrastructure to identify respiratory disease pathogens and evaluate new diagnostic and control measures.

Strong, laboratory-based surveillance programs are needed to quickly identify new problems. The surveillance programs must be supported by fast, accurate diagnostic laboratory tests. Surveillance data must then be used to direct the development and evaluation of new interventions, particularly vaccines.

Acknowledgments

We acknowledge the contributions of Drs. Richard Haberberger and Gale Chapman, Tom Ferguson, Tim Driscoll, David Trump, Christie Beadle, and Theodore Woodward.

Collaborators in Department of Defense surveillance for respiratory disease pathogens include Patrick Kelley, Lisa Keep, Ramy Mahmoud, Annette Hamilton, Maria Hook, Beverly Watts, Mills McNeill, Laura Trent, Linda Canas, William Corr III, Sandra Williams, Kelly McKee Jr., Debra Prantl, Rose Marie Hendrix, Jane Lindner, Johnnie Conolly, Michael Escalara, Gerald Sandifer, Robert Greenup, Barbara Workman, Denise Clayton, David Niebuhr, Gretchen Demmin, Maritza Johnson, Jeffrey Gunzenhauser, Mary Meyers, Mark Kotepeter, Crystal Chatman-Brown, Alice Washington, Megan Ryan, Thomas Hatley, Becky Christian, Julie Wohlrabe, Sharon Urban, Stephanie Thorn, Dennis Butterworth, James Bean, Beverly Southerland, John Newsome, Edward Gastaldo, Juan Rivas, Walter Cole, Roger Batchelor, Marianne Jesse, Jim Blanks, Roger Gibson, Ron Hale, Royce Brockett, Pulak Goswami, Marieta Malasig, Marie Hudspeth, Julie Hochwalt, Mary Sorenson, Jason Unruh, Paul Sato, Colleen McDonough, Heather Taylor, Rosana Magpantay, Tuan Pham, Chris Barrozo, Pam

Plobette, Debbie Kamens, Jeff LeClair, Cassandra Morn, Farukh Khambaty, Janet Yother, and Susan Hollingshead.

This represents report no. 98-22, supported by the Office of Naval Research, Washington, DC, under DoD/HA reimbursable - 6609.

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